Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients

Journal of Clinical Lipidology (2010) 4, 272–278

Journal of Clinical Lipidology

Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients

Maurizio Averna, MD, Augusto Zaninelli, MD, Cristina Le Grazie, MD*, Gian Franco Gensini, MD

Department of Clinical Medicine and Emerging Diseases, Policlinico Paolo Giaccone, University of Palermo, Palermo, Italy (Dr. Averna); Department of Internal Medicine and Cardiology, University of Florence, Florence, Italy (Drs. Zaninelli and Gensini); and Medical and Scientific Affairs, Merck Sharp & Dohme, Centro Direzionale Milano Due, Palazzo Borromini 20090 Segrate, Milano, Italy (Dr. Le Grazie)

KEYWORDS:
Cholesterol absorption inhibitor;
Coronary heart disease;
Ezetimibe;
Lipids;
Simvastatin

BACKGROUND: Reducing low-density lipoprotein cholesterol (LDL-C) is the primary goal of therapy in patients with hypercholesterolemia and coronary heart disease (CHD).

METHODS: This double blind placebo-controlled study enrolled patients 18 to 75 years of age with primary hypercholesterolemia and established CHD who were taking a stable daily dose of simvastatin 20 mg. Patients were randomized to ezetimibe/simvastatin 10/20 mg (eze/simva; n = 56) or simvastatin 40 mg (simva; n = 56) for 6 weeks. Percent change from baseline in LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were assessed by use of the Student *t* test. The percent of patients achieving LDL-C less than 100 mg/dL (<2.6 mmol/L) or less than 80 mg/dL (<2.0 mmol/L) was analyzed via logistic regression with terms for treatment, baseline LDL-C, age, and gender.

RESULTS: Baseline characteristics were similar between groups. Treatment with eze/simva combination resulted in significantly greater reductions in LDL-C, total cholesterol, and triglycerides versus doubling the dose of simva to 40 mg (all $P < .01$). Significantly more patients achieved LDL-C less than 100 mg/dL (<2.6 mmol/L) and less than 80 mg/dL (<2.0 mmol/L) with ezetimibe/simvastatin versus doubling the dose of simva to 40 mg (73.2% vs 25.0%; $P < .001$) for simvastatin. Changes in HDL-C were similar between treatments. Both treatments were generally well tolerated.

CONCLUSION: In high-risk CHD patients with hypercholesterolemia, treatment with eze/simva combination resulted in significantly greater reductions in LDL-C, total cholesterol and triglycerides, as well as greater achievement of recommended LDL-C targets, compared with doubling the simvastatin dose to 40 mg over the 6-week period. (Clinical trial registration number: NCT00423579)

Reducing the level of low-density lipoprotein cholesterol (LDL-C) is the primary goal for therapeutic intervention in patients with hypercholesterolemia and coronary heart disease (CHD).[1–3] The recommended LDL-C treatment target for patients at moderately high or high risk for CHD is less than 100 mg/dL (<2.6 mmol/L), with less than 70 mg/dL (1.8 mmol/L) as an optional therapeutic target in the United States[1,4,5]; in Europe, the targets are similar: less than 97 mg/dL (<2.5 mmol/L) with an optional goal of less than 80 mg/dL (<2.0 mmol/L).[6] The 2009 Canadian Cardiovascular Society guidelines recommend an LDL-C target less than 80 mg/dL (<2.0 mmol/L) or a 50% reduction in LDL-C.[3]

* Corresponding author.
E-mail address: mariacristina.legrazie@fastwebnet.it
Submitted March 12, 2010. Accepted for publication May 20, 2010.

1933-2874/$ - see front matter © 2010 National Lipid Association. All rights reserved.
doi:10.1016/j.jacl.2010.05.002

If therapeutic lifestyle changes are not sufficient, HMG CoA reductase inhibitors (statins) are the first line of therapy for lowering of LDL-C. Statins have been shown to effectively lower LDL-C[7]; however, a considerable number of patients receiving moderate doses of statins do not achieve LDL-C treatment targets.[6,8,9] Intensive therapy with greater doses of statins may confer greater reductions in LDL-C, but some patients may not tolerate high-dose statins.[10] Moreover, the incidence of abnormalities in liver function or myopathy may increase in a dose-dependent manner with this class of drugs;[11] and even with a high dose, treatment goals are not met in some patients.[9]

The use of a combination of drugs that have a dual mechanism of action in cholesterol regulation may be an effective means of reducing LDL-C in patients who are not attaining targets with statin monotherapy.[12,13] Treatment with ezetimibe, a known inhibitor of cholesterol absorption, combined with a statin results in significantly greater reductions in LDL-C and other lipid parameters and greater LDL-C target attainment compared with statin monotherapy (pooled doses) in patients with hypercholesterolemia.[14–19] These significantly greater effects have also been shown with ezetimibe added to the moderate doses of statins compared with doubling the dose of the same statin in moderately-high risk and high-risk CHD patients and in diabetic patients.[20–22] This study assessed the lipid-altering efficacy and tolerability of 6 weeks of treatment with ezetimibe/simvastatin 10/20 mg versus doubling the dose of simvastatin to 40 mg in patients with hypercholesterolemia and established CHD who had not achieved the National Cholesterol Education Program Adult Treatment Panel III recommended LDL-C target less than 100 mg/dL while being treated with a daily dose of simvastatin 20 mg.

Methods

Study design

This was a multicenter, randomized, parallel-groups, double-blind, placebo-controlled study conducted at 23 sites in Italy from July 2006 to March 2008. The protocol (Protocol 4039) was reviewed and approved by an Independent Ethics Committee at each participating center, and patients provided written informed consent prior to any study-related procedure being started. The study was conducted under the provisions of the Declaration of Helsinki and in accordance with the International Conference on Harmonization Consolidated Guideline on Good Clinical Practice.

Patients

This study enrolled men and women 18 to 75 years of age with documented CHD (including stable angina with evidence of ischemia on exercise testing, history of myocardial infarction, percutaneous transluminal coronary angioplasty, atherothrombotic cerebrovascular disease, unstable angina or non-Q wave myocardial infarction; symptomatic peripheral vascular disease) who were taking a stable daily dose of simvastatin 20 mg for 6 weeks with good compliance (80% of daily doses for the 6 weeks before baseline visit) and had LDL-C concentration greater than 100 mg/dL (>2.6 mmol/L) to 160 mg/dL or less (≤4.1 mmol/L). Patients were instructed to maintain a cholesterol-lowering diet and an exercise program for at least 4 weeks before screening and during the study. Patients were required to have triglyceride concentrations less than 350 mg/dL (<3.99 mmol/L), liver transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) and creatine phosphokinase (CK) less than 50% above the upper limit of normal (ULN) with no active liver disease, and hematology, blood chemistry, and urinalysis within normal limits. Women of childbearing potential were required to use effective birth control.

Patients were excluded if they had class III or IV congestive heart failure; uncontrolled cardiac arrhythmia; recent (within 3 months of randomization) myocardial infarction, acute coronary insufficiency, coronary artery bypass surgery, or angioplasty; unstable or severe peripheral artery disease; newly diagnosed or unstable angina pectoris; uncontrolled hypertension (treated or untreated); uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; impaired renal function (creatinine >2.0 mg/dL) or nephrotic syndrome; or were taking any lipid-lowering agents, fibrates, resins or niacins, or prescription and/or over-the-counter-drugs with the potential for significant lipid effects (other than study drug) or with potential drug interactions with the statins.

Randomization and blinding

Patients were randomized according to a computer-generated randomization schedule into two treatment sequences by the use of a 1:1 ratio to receive either eze/simva 10/20 mg and simvastatin 40 mg placebo or eze/simvastatin 10/20 mg placebo and simvastatin 40 mg for 6 weeks. The study medications were packaged as 1 bottle of eze/simva 10/20 mg (active or placebo) and 1 bottle of simvastatin 40 mg (active or placebo). Blinding was maintained until after study completion and database closure. Patient compliance was assessed by tablet count returned at the end of study. Compliance less than 70% was considered a major protocol violation.

Efficacy measures

The primary efficacy variable was the percentage change in LDL-C from baseline after 6 weeks of treatment. Secondary efficacy variables were the percent of patients achieving LDL-C less than 100 mg/dL (<2.6 mmol/L) or LDL-C less than 80 mg/dL (<2.0 mmol/L); percent change from baseline in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides after 6 weeks of treatment. The basic lipid panel assessment was conducted

at a central laboratory (Centro Diagnostico EXACTA, Verona, Italy). LDL-C measurements were calculated by the Friedewald equation.[23]

Safety and tolerability

Adverse events were monitored at each visit and summarized by system organ class and specific adverse experience term. Laboratory tests included complete blood count, total protein, albumin, calcium, inorganic phosphorus, fasting plasma glucose, blood urea nitrogen, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, gamma glutamyl transpeptidase, serum creatinine, thyroid-stimulating hormone (baseline only), HbA_{1c}, sodium, potassium, chloride, CK; and urinalysis. The analysis of laboratory parameters was conducted at a cental laboratory (Centro Diagnostico EXACTA, Verona, Italy).

Statistics

Estimating a common standard deviation equal to 22.0 and choosing $\alpha = 0.05$ and $\beta = 0.10$, it was determined that a sample size of 55 subjects in each group would confer a 90% power to detect a treatment group difference in LDL-C change means of −14%, assuming that the common standard deviation was 22.0 with the use of a two-group *t*-test with a 0.05 two-sided significance level.

The primary efficacy end points were assessed in the intention-to-treat population, which included all subjects who were randomized, had taken at least one dose of study drug and had at least one measurement at baseline and after the start of treatment. Percent change from baseline in LDL-C, total cholesterol, HDL-C, and triglyceride levels were assessed with the use of the Student *t* test for independent samples using an alpha of 0.05 (two-tailed) as cut-off for significance. Percentage of patients achieving LDL-C targets was analyzed with a logistic regression model with terms for treatment, baseline LDL-C level, age (<65, ≥65), and gender. Odds ratio estimates derived from the logistic regression model and 95% confidence intervals were used to quantify the treatment effect. The safety population included all randomized patients who took at least one dose of study drug. The incidence of adverse events was compared between treatments by use of the Fisher exact test with Yates correction if applicable.

Results

The flow of patients through the study is summarized in Figure 1. Of the 182 patients that were screened, 60 were randomized to receive eze/simva 10/20 mg, and 60 were randomized to receive simvastatin 40 mg. A total of eight patients discontinued from the study after randomization. Reasons for discontinuation were seven protocol violations (four in the eze/simva group and three in the simvastatin group), and one adverse event (simvastatin group).

Baseline characteristics are summarized in Table 1. All patients were white, and the majority were male (53.6% in the eze/simva group and 57.1% in the simva 40 mg group). The mean age (± SD) was 61 (± 8.4) years in the eze/simva group and 62 (± 7.8) years in the simva 40 mg group. Demographic data, medical history, cardiovascular risk factors, and baseline values of all efficacy and safety parameters were similar between the two treatment groups. The mean baseline LDL-C was 125.9 (± 16.3)

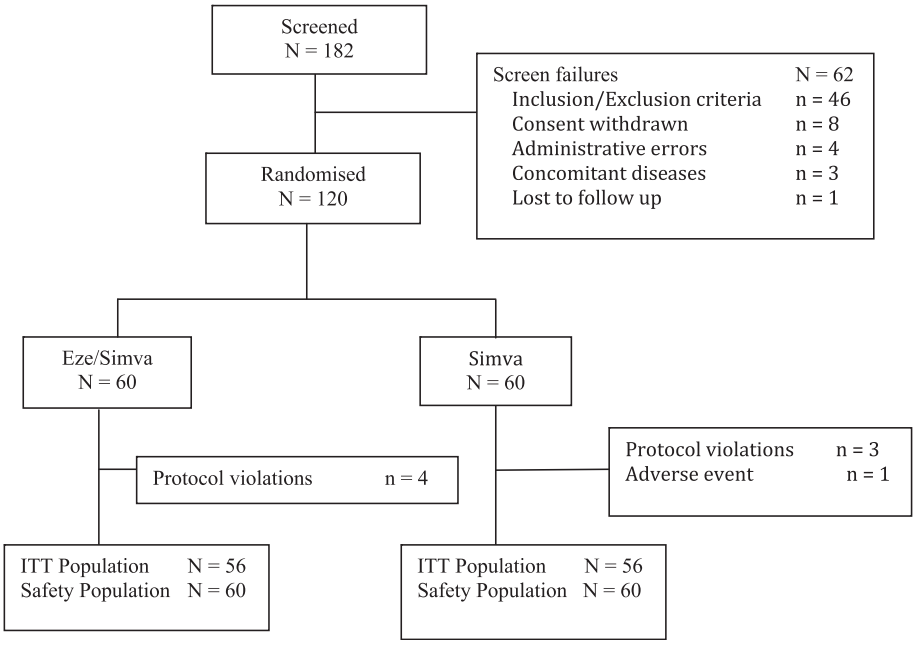


Figure 1 Flow of patients through the study. Eze/Simva = ezetimibe/simvastatin 10/20 mg; ITT = intention to treat; simva 40 = simvastatin 40 mg.

mg/dL in the eze/simva 10/20 treatment group and 128.8 (± 16.6) in the simvastatin 40 mg group. Cerebrovascular disease was the most common form of cardiovascular disease reported at baseline, with 22 (39.3%) patients in the eze/simva 10/20 mg group and 20 (35.7%) patients in the simva 40 mg group (Table 1).

After 6 weeks, treatment with combination eze/simva 10/20 mg resulted in a significantly greater reduction in mean LDL-C level compared with doubling the dose of simvastatin to 40 mg (−27% vs −12%: $P < .001$; Fig. 2). In addition, the percentage of patients achieving LDL-C less than 100 mg/dL (<2.6 mmol/L) was significantly greater with eze/simva 10/20 treatment versus doubling the dose of simva to 40 mg (73% vs 25%: $P < .001$; Fig. 3). The odds of achieving LDL-C less than 100 mg/dL was 8.20 in favor of eze/simva (95% confidence interval: 3.52−19.11; $P < .001$) and was dependent on baseline LDL-C value but not age or gender. The percentage of subjects who achieved LDL-C less than 80 mg/dL (<2.0 mmol/L) after 6 weeks was significantly greater for the eze/simva 10/20 group compared with the simva 40 mg group (21% vs 4%: $P = .010$; Fig. 3). The odds of achieving LDL-C less than 80 mg/dL was 7.36 in favor of eze/simva (95% confidence interval: 1.56−34.66; $P = .0158$) and was dependent on baseline LDL-C value, but not age or gender.

The percent reduction in total cholesterol was significantly greater with eze/simva 10/20 mg combination treatment compared with doubling simva to 40 mg after 6 weeks of treatment (−16.9% vs −7.5%: $P < .001$; Fig. 4). Mean % changes in triglycerides and HDL-C were similar between treatment groups (Fig. 4).

Safety and tolerability

A summary of safety results is shown in Table 2. The proportion of patients who reported adverse events was similar between treatment groups ($P = .9999$), with few discontinuations caused by adverse events (only one patient in the simva 40-mg group). No differences between groups were observed in the number and rate of drug-related events, which were reported in 11.75% of patients in the Eze/Simva group and in 6.8% of patients in the Simva group ($P = .5269$). One serious adverse event was reported (transient ischemic attack) that was considered nondrug related. There were no reports of increased ALT or AST ≥ 3X ULN or CK ≥ 5X ULN, and no deaths occurred at any time during the study in either treatment group.

Discussion

The results of this study demonstrated that ezetimibe 10 mg combined with simvastatin 20 mg produced significantly greater reductions in LDL-C and total cholesterol compared with doubling the dose of simvastatin to 40 mg in patients with hypercholesterolemia and CHD. Furthermore, a significantly greater percentage of patients achieved

Table 1 Baseline patient characteristics

	Eze/Simva 10/20 mg (n = 56)	Simva 40 mg (n = 56)
Demographics		
Age, Mean years (SD)	61 (8.4)	62 (7.8)
Females, n (%)	26 (46.4)	24 (42.9)
Body mass index, kg/m^2, mean (SD)	26.6 (3.2)	26.3 (2.6)
Concomitant medications, n (%)	49 (87.5)	47 (83.9)
Hypertension, n (%)	30 (50.0)	28 (46.7)
Baseline lab values, mean (SD)		
LDL-C, mg/dL	125.9 (16.3)	128.0 (16.6)
Total C, mg/dL	201.2 (22.6)	201.7 (19.4)
HDL-C, mg/dL	50.5 (11.4)	48.8 (9.2)
Triglycerides, mg/dL	120.2 (48.4)	124.0 (41.9)
Fasting plasma glucose, mg/dL	99.5 (9.7)	100.8 (13.8)
AST, U/L	21.5 (5.4)	20.9 (4.5)
ALT, U/L	23.5 (10.1)	23.6 (7.6)
CK, U/L	106.4 (44.6)	113.1 (45.9)
Prevalence of cardiovascular diseases, n (%)		
Cerebrovascular disease	22 (39.3)	20 (35.7)
Peripheral vascular disease	18 (32.1)	17 (30.4)
Ischemic heart disease	13 (23.2)	15 (26.8)
Cerebrovascular disease + PAD	2 (3.6)	4 (7.0)
Cerebrovascular disease + ischemic heart disease	1 (1.8)	0 (0.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine phosphoKinase; HDL-C, high-density lipoprotein.
There were no significant differences between groups.

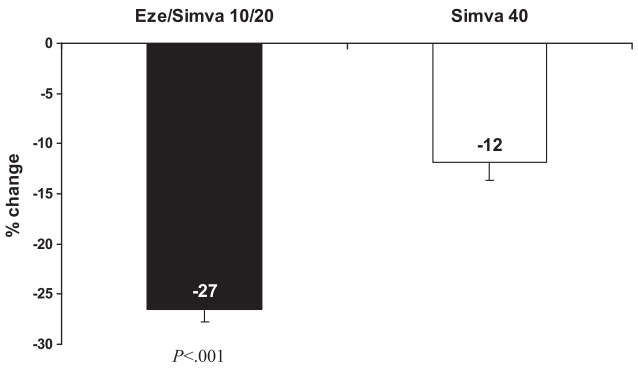
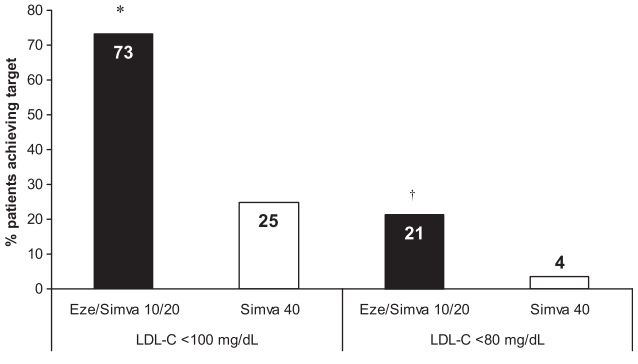


Figure 2 Percent change from baseline in low-density lipoprotein cholesterol (LDL-C) after 6 weeks of treatment. Bars represent standard error. Eze/Simva = ezetimibe/simvastatin 10/20 mg; simva 40 = simvastatin 40 mg.

National Cholesterol Education Program Adult Treatment Panel III recommended LDL-C targets less than 100 or less than 80 mg/dL after 6 weeks of treatment with the combination of eze/simva 10/20 mg compared with doubling the dose of simva to 40 mg. The results of this study were generally consistent with previous studies of similar design and duration conducted in patients with hypercholesterolemia and CHD,[20,21,24–28] but this study is the first to compare these two strategies in subjects with CHD that excluded those with diabetes.

Failure to achieve LDL-C targets is particularly marked in high-risk patients with hypercholesterolemia and CHD.[29] Moderate doses of statin may not always be sufficient for achievement of LDL-C treatment targets,[6,8,9] and high-dose statins may not be tolerated by all patients.[10]

Recent investigations have reported that alterations in cholesterol homeostasis (namely high cholesterol absorption and low cholesterol synthesis) are associated with increased CVD risk.[30] However, the search for markers that could predict the extent of the response to statins in terms of LDL-C reduction has not yet produced unequivocal and clinically applicable results. The LDL-C lowering after



*Odds ratio=8.20 (95% confidence interval: 3.52-19.11)
†Odds ratio=7.36 (95% confidence interval: 1.56-34.66)

Figure 3 Percent of patients achieving low-density lipoprotein cholesterol (LDL-C) < 100 mg/dL (<2.6 mmol/L) or <80 mg/dL (<2.0 mmol/L) after 6 weeks of treatment. Eze/Simva = ezetimibe/simvastatin 10/20 mg; simva 40 = simvastatin 40 mg.

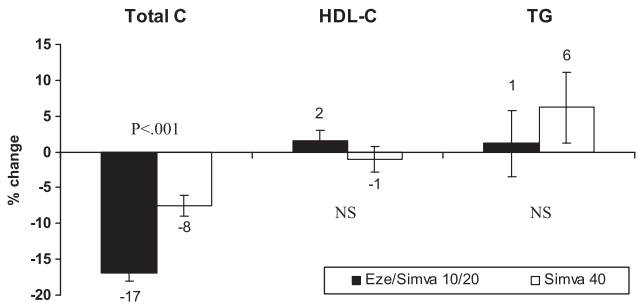


Figure 4 Percent change from baseline in total cholesterol (Total C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) after 6 weeks of treatment. Eze/Simva = ezetimibe/simvastatin 10/20 mg; simva 40 = simvastatin 40 mg.

statin treatment with appropriate potency, dose and duration is probably at present the only way to assess if a patient is a "poor responder."

It has been suggested that reducing cholesterol absorption with the use of ezetimibe treatment combined with statins to lower hepatic cholesterol synthesis may be a practical approach to intensive lipid management and goal achievement compared with treatments that reduce synthesis alone (ie, statins) in patients with hypercholesterolemia who have not achieved LDL-C targets on statin monotherapy.[31] This may be of particular relevance in high cardiovascular risk patients in whom between-group LDL-C reductions in favor of eze/simva were demonstrated in patients who were not at target on prior statin therapy.[32] In that study, the addition of ezetimibe to simvastatin 10 or 20 mg for 6 weeks resulted in an approximately two-fold greater magnitude reduction in LDL-C and greater target attainment compared with rosuvastatin 10 mg.[32] Similarly, the results of the present study showed a nearly two-fold magnitude of difference between treatment groups, confirming the greater efficacy for lowering LDL-C and total cholesterol through the dual mechanism of blocking cholesterol synthesis and absorption compared with blocking cholesterol synthesis alone.

Both treatments had similar tolerability profiles during the study period. There were no reports of increased ALT or AST ≥3X ULN nor CK ≥10 ULN in either treatment group during the study. Accordingly, neither the addition of ezetimibe to simvastatin 20 mg nor doubling the dose of simvastatin to 40 mg resulted in reports of myopathy or rhabdomyolysis. These results are consistent with expectations for these drugs at the doses given and with previous trials in this patient population.[24,25,33,34] Although the incidence of serious adverse events was low, this study was relatively small and not powered nor of sufficient duration to assess the prevalence of rare adverse events. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial raised questions about the possibility of an increase in the incidence of cancer with the addition of ezetimibe to statin therapy,[35,36] although this has not been observed in data from a large postmarketing analysis, as well as clinical and nonclinical study databses. A meta-analysis of cancer

Table 2 Summary of safety data

Number of patients (%)	Eze/Simva 10/20 mg (n = 60)	Simva 40 mg (n = 60)	*P* value
With AEs	13 (21.7)	13 (21.7)	NS
With treatment-related AEs	7 (11.7)	4 (6.8)	NS
Discontinued due to AEs	0	1 (1.7)	NS
Discontinued due to treatment-related AEs	0	0	
Serious AEs	0	1 (1.7)*	NS
Serious treatment-related AEs	0	0	
ALT/AST $\geq 3\times$ULN	0	0	
CK $\geq$ 5-10$\times$ULN elevation	0	0	

AEs, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase; NS, not significant; ULN, upper limit of normal.

*Transient ischemic attack—not drug related.

data from the Study of Heart and Renal Protection (SHARP) that included 9264 patients and Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) with 11,353 patients demonstrated no credible evidence of any adverse effect of ezetimibe on rates of cancer, suggesting that the observation in the SEAS trial was a chance occurrence.[37] Longer-term follow-up may elucidate the balance of risks and benefits of combining ezetimbe with statin therapy.

In conclusion, treatment with combination eze/simva results in significantly greater reductions in LDL-C levels and attainment of LDL-C targets than doubling the dose of simvastatin. The combination treatment was generally well tolerated. These results provide further evidence that inhibiting dual pathways of cholesterol metabolism may be an effective approach to LDL-C reduction and treatment in high-risk, non-diabetic patients with hypercholesterolemia and CHD who have not achieved treatment targets with statins alone. Reduced ischemic cardiovascular event risk has been associated with decreases in lipoprotein components after 1 year of ezetimibe plus simvastatin treatment.[38] Whether these results will translate into clinical benefit in patients at high risk of CHD awaits results of additional outcome studies.

Financial disclosures

This study was funded by Schering-Plough Spa, Italy. At the time that the study was conducted, Dr. Le Grazie was an employee of Schering-Plough.

Acknowledgments

The authors wish to acknowledge Dr. Mary E. Hanson of Merck & Co., Inc. for assistance in the writing and preparation of the manuscript. The DIALOGUE Study Group included the following physicians and recruiting centers: Prof. Gianfranco Gensini, Firenze; Prof. Maurizio Averna, Palermo; Prof. Noe Battistini, Siena; Prof. Adriana Branchi, Milano; Dr. Carlo Cappelletti, Firenze; Prof. Antonio Capurso, Bari; Dr. Vinvenzo Siragusa, Palermo; Dr. Salvatore Di Rosa, Palermo; Dr. Tiziana Sampietro, Pisa; Prof. Renato Fellin, Ferrara; Prof. Carlo Gandolfo, Genova; Prof. Renato Lauro, Roma; Prof. Elmo Mannarino, Perugia; Prof. Enzo Manzato, Padova; Prof. Andrea Mezzetti, Chieti Scalo; Dr. Anna Cavallini, Pavia.

References

1. Expert panel on detection evaluation and treatment of high blood cholesterol in adults. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
2. JBS 2. Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91(Suppl 5):v1–52.
3. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult—2009 recommendations. *Can J Cardiol*. 2009;25:567–579.
4. Assmann G, Carmena R, Cullen P, et al. Coronary heart disease: reducing the risk: a worldwide view. International Task Force for the Prevention of Coronary Heart Disease. *Circulation*. 1999;100: 1930–1938.
5. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. 2008;31:811–822.
6. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil*. 2007;14(Suppl 2):S1–S113.
7. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
8. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil*. 2009;16:121–137.
9. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the

percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med*. 2000;160:459–467.
10. Gotto AM Jr. Statins, cardiovascular disease, and drug safety. *Am J Cardiol*. 2006;97:3C–5C.
11. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr Opin Lipidol*. 2007;18:401–408.
12. Ballantyne CM. Rationale for targeting multiple lipid pathways for optimal cardiovascular risk reduction. *Am J Cardiol*. 2005;96:14K–19K.
13. Matthan NR, Pencina M, Larocque JM, et al. Alterations in cholesterol absorption and synthesis characterize Framingham offspring study participants with coronary heart disease. *J Lipid Res*. 2009;1927–1935.
14. Ballantyne CM, Weiss R, Moccetti T, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). *Am J Cardiol*. 2007;99:673–680.
15. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol*. 2002;40:2125–2134.
16. Davidson MH, Ballantyne CM, Kerzner B, et al. Efficacy and safety of ezetimibe coadministered with statins: randomised, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia. *Int J Clin Pract*. 2004;58:746–755.
17. Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *Am J Cardiol*. 2003;91:418–424.
18. Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Eur Heart J*. 2003;24:717–728.
19. Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. *Curr Med Res Opin*. 2007;23:2009–2026.
20. Conard SE, Bays HE, Leiter LA, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. *Am J Cardiol*. 2008;102:1489–1494.
21. Leiter LA, Bays H, Conard S, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. *Am J Cardiol*. 2008;102:1495–1501.
22. Gaudiani LM, Lewin A, Meneghini L, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. *Diabetes Obes Metab*. 2005;7:88–97.
23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
24. Barrios V, Amabile N, Paganelli F, et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. *Int J Clin Pract*. 2005;59:1377–1386.
25. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J*. 2004;148:447–455.
26. Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. *Am J Cardiol*. 2004;93:1487–1494.
27. Constance C, Westphal S, Chung N, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2007;9:575–584.
28. Pearson T, Ballantyne C, Sisk C, Shah A, Veltri E, Maccubbin D. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. *Am J Cardiol*. 2007;99: 1706–1713.
29. Foley KA, Simpson RJ Jr., Crouse JR III, Weiss TW, Markson LE, Alexander CM. Effectiveness of statin titration on low-density lipoprotein cholesterol goal attainment in patients at high risk of atherogenic events. *Am J Cardiol*. 2003;92:79–81.
30. Matthan NR, Larocque JM, Pencina M, D'Agostino RB, Schaefer EJ, Lichtenstein AH. Increased cholesterol absorption and decreased cholesterol synthesis characterize Framingham Offspring Study participants with coronary heart disease. *Circulation 112*. 2005;(17 Suppl S): U892–U893.
31. Catapano AL. Perspectives on low-density lipoprotein cholesterol goal achievement. *Curr Med Res Opin*. 2009;25:431–447.
32. Farnier M, Averna M, Missault L, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy - The IN-CROSS study. *Int J Clin Pract*. 2009;63:547–559.
33. Zocor (simvastatin) tablets [package insert]. Whitehouse Station, NJ: Merck & Co. Inc; 2008.
34. Vytorin (ezetimibe/simvastatin) [package insert]. North Wales, PA: Merck/Schering-Plough Pharmaceuticals; 2009.
35. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–1356.
36. Alsheikh-Ali AA, Karas RH. Ezetimibe, and the combination of ezetimibe/simvastatin, and risk of cancer: a post-marketing analysis. *J Clin Lipidol*. 2009;3:138–142.
37. Peto R, Emberson J, Landray M, et al. Analyses of cancer data from three ezetimibe trials. *N Engl J Med*. 2008;359:1357–1366.
38. Holme I, Boman K, Brudi P, et al. Observed and predicted reduction of ischemic cardiovascular events in the Simvastatin and Ezetimibe in Aortic Stenosis Trial. *Am J Cardiol*. 2010;105:1802–1808.